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EXAMINER
ANGELL, JON E

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 06/04/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/937,643	PHILLIPS ET AL.	
	Examin r	Art Unit	
	J. Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26-56 and 66-68* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-56 and 66-68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 September 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This Action is in response to the communication filed on 3/24/03, as Paper No. 14. The amendment has been entered. Claims 1-25 and 57-65 have been cancelled. Claims 26, 36, 40, 48 have been amended. Claims 26-56 and 66-68 are currently pending in the application and are addressed herein. It is noted that the Applicants have stated in the response filed 3/24/03 that 51-56 are not pending; however, claims 51-56 have never been cancelled and are currently pending in the application.

Continued Examination Under 37 CFR 1.114

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/24/03 has been entered.

Double Patenting

3. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

4. Claims 26-56 and 66-68 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 3-30 of U.S. Patent No. 6,326,357 (hereafter '357) in view of Morales (Journ. Urology, Vol. 153, p. 1706-1710, 1995).

5. The instant claims are drawn to methods of treating prostate cancer comprising administering to a subject having prostate cancer a composition comprising mycobacterial DNA, such as M. phlei DNA, and a pharmaceutically acceptable carrier, such as the mycobacterial cell wall, wherein the mycobacterial DNA is obtained from disrupted mycobacterium using DNase-free reagents in order to at least partially preserve the DNA.

6. The '357 patent claims a method for treating cancer by administering to a patient cancer a composition comprising M. phlei DNA preserved and complexed on the M. phlei cell wall (see claims 3-30). Looking to the specification of '357 to determine how the M. phlei DNA was prepared, the specification discloses, "The M. phlei are disrupted and the solid components are deproteinized, delipidated, and washed. DNase-free reagents are used to minimize M-DNA degradation during preparation." (See col. 3, lines 50-56).

The '357 patent does not indicate that the M. phlei-DNA composition can be used to treat prostate cancer.

However, Morales teaches that fractionated and deproteinized emulsions of M. phlei cell walls (which would necessarily comprise M. phlei DNA) have antineoplastic effects on prostate cancer cells (e.g., see p. 1706, col. 2, lines 6-8).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of filing that the method of treating cancer using an M. phlei-DNA composition claimed in the '357 patent could be used to treat prostate cancer.

One of ordinary skill would have been motivated to use the composition of '357 to treat prostate cancer because Morales teaches that M. phlei cell wall complex (which comprises M. phlei DNA) can be used to treat prostate cancer. Therefore, the instant claims are obvious variants of the invention claimed in US patent 6,326,357.

7. Claims 26-56 and 66-68 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-24 of U.S. Patent No. 6,329,347 (hereafter '347) in view of Morales (Journ. Urology, Vol. 153, p. 1706-1710, 1995).

8. The instant claims are drawn to methods of treating prostate cancer comprising administering to a subject having prostate cancer a composition comprising mycobacterial DNA, such as M. phlei DNA, and a pharmaceutically acceptable carrier, such as the mycobacterial cell wall, wherein the mycobacterial DNA is obtained from disrupted mycobacterium using DNase-free reagents in order to at least partially preserve the DNA.

9. The '347 patent claims a method for treating bladder cancer by administering to a patient cancer a composition comprising M. phlei DNA preserved and complexed on the M. phlei cell wall (see claims 1-24). Looking to the specification of '357 to determine how the M. phlei DNA was prepared, the specification discloses, "The M. phlei are disrupted... the solid components are deproteinized, delipidated, and washed. DNase-free reagents are used to minimize M-DNA degradation during preparation." (See col. 3, line 63 through column 4, line 2).

The '347 patent does not indicate that the M. phlei-DNA composition can be used to treat prostate cancer.

However, Morales teaches that fractionated and deproteinized emulsions of M. phlei cell walls (which would necessarily comprise M. phlei DNA) have antineoplastic effects on prostate cancer cells (e.g., see p. 1706, col. 2, lines 6-8).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of filing that the method for treating bladder cancer using an M. phlei-DNA composition claimed in the '347 patent could be used to treat prostate cancer.

One of ordinary skill would have been motivated to use the composition of '357 to treat prostate cancer because Morales teaches that M. phlei cell wall complex (which comprises M. phlei DNA) can be used to treat prostate cancer. Therefore, the instant claims are obvious variants of the invention claimed in US patent 6,329,347.

Claim Rejections - 35 USC § 112

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 66-68 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

12. Claim 66 recites the limitation "the amount of M-DNA" in line 9. There is insufficient antecedent basis for this limitation in the claim because "M-DNA" is not recited anywhere else

in the claim. It is noted that claim 66 does recite "B-DNA" and amending the claim to recite "the amount of B-DNA" rather than "the amount of M-DNA" would obviate this rejection.

13. Similarly claims 67 and 68 recite "the amount of M-DNA", and there is no antecedent basis for the term "M-DNA". Amending the claims to recite "B-DNA" rather than "M-DNA" would obviate this rejection.

Claim Rejections - 35 USC § 112, first paragraph

14. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15. Claims 26-56 and 66-68 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

> Methods for inhibiting prostate tumor growth comprising the administration of a composition comprising:
>
> (a) mycobacterial DNA obtained from a disrupted mycobacterium using DNase-free reagents in order to at least partially preserve the DNA; and,
>
> (b) a pharmaceutically acceptable carrier
>
> to an animal or human harboring a prostate tumor, wherein said mycobacterial DNA is M. phlei-DNA, and wherein said composition is directly delivered into said prostate tumor in an amount effective to inhibit the growth of said prostate tumor.

Does not reasonably provide enablement for the full scope encompassed by the claims. Specifically, the claims are not enabled for general (e.g., systemic) delivery of a composition comprising any mycobacterial DNA. The specification does not enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,
"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The instant claims are drawn to methods for treating prostate cancer using a composition comprising mycobacterial DNA. Therefore, the general nature of the invention is cancer therapy. Although the claims do not necessarily encompass gene therapy, many of the problems associated with gene therapy (such as delivery) are also applicable to the instant methods.

The breadth of the claims

The claims are broad, considering the claims encompass a method for treating prostate cancer by administering by any means (e.g., systemic administration) a therapeutic composition comprising DNA from any species of mycobateria, and a pharmaceutically acceptable carrier.

The unpredictability of the art and the state of the prior art

It is recognized in the relevant prior art that in order for a pharmaceutical composition comprising a therapeutic nucleic acid to be effective, it must be directly delivered to the target site.

Regarding the administration of the therapeutic nucleic acid to a part of the body other than site of the wound, it is well established in the art that delivery is one of the key problems associated with gene therapy. For instance, regarding gene therapy in general, Anderson (Nature 1998; 392(suppl):25-30) teaches,

> The challenge is to develop gene therapy as an efficient and safe drug delivery system. The goal is more difficult to achieve than many investigators had predicted... The human body has spent many thousands of years learning to protect itself from the onslaught of environmental hazards, including the incorporation of foreign DNA into its genome. (See p. 25, second paragraph). The ultimate goal of gene therapy research is the development of vectors that can be injected, will target specific cells, will result in safe and efficient gene transfer into a high percentage of those cells, will insert themselves into appropriate regions of the genome (or will persist as stable episomes), will be regulated be either by administered agents or by the body's own physiological signals, will be cost effective and will cure disease. (See p. 30, first paragraph).

Crystal (Science 1995; 270:404-410) also indicates some of the problems regarding gene therapy in general. Specifically, regarding the obstacles of human gene transfer, Crystal teaches, "The [gene transfer] vector (should) be specific for its target, not recognized by the immune system..." (See p. 409, column 2 under "The perfect vector").

Finally, regarding the delivery of gene therapy vectors to tumors, but applicable to the specific delivery of all gene therapy molecules, Greco (Frontiers in Biosci. 2002; 7:d1516-1524) teaches,

> The administration of gene therapy vectors requires that they be not only targeted, but also protected from degradation, sequestration or immune attack, in order to reach the appropriate sites for transfection. Although some success has been reported for naked DNA, efficient delivery has been restricted to intratumoral injection. (See p. 1517, paragraph bridging columns 1-2).

Indicating that direct delivery of the nucleic acid to the desired site of transfection is critical for effective delivery of the therapeutic nucleic acid composition.

It is noted that although the instant claims are not drawn to gene therapy, per se, the claims do encompass administration of a therapeutic composition comprising nucleic acid as the therapeutic agent. Therefore, the problems recognized in the prior art and indicated above are applicable to the instant claims because the instant composition would also be subject degradation or attack by the host's immune system before the composition could have an anti-proliferative effect on the target prostate tumor.

Regarding problems specifically related to pharmaceutical administration of mycobacterial DNA/cell wall compositions for the treatment of cancer, Morales (Journ. Urol. 153:1706-1710; 1995) teaches, "successful immunotherapy of solid neoplasms has been an elusive goal" (see p1706, first paragraph). In addition to the general unpredictable nature of mycobacterial compositions for the treatment of cancer, Morales also teaches a number of specific problems. For instance, Morales teaches that although administration of mycobacteria phlei cell wall (MCW) by intratumoral administration results in regression of established prostate tumors, "the response, however, depends initially on the route of administration. The intraperitoneal route was found to be not only in effective, but detrimental." (See p. 1709, bottom, first column). Furthermore Morales teaches, "the intraperitoneal administration of MCW did not alter tumor-growth kinetics... the rats receiving MCW by this route became lethargic, anorexic and exhibited considerable hair loss." (See p. 1707, middle of first column).

Additionally, Morales teaches that prostate tumors were unresponsive to intralesional treatment with an emulsion of bacilli Calmette-Guerin (BCG) cell walls (see Morales, p. 1706,

col. 2, lines 1-3). It is noted that the BCG cell wall emulsion was known to be an effective treatment for bladder cancer (see Morales, p. 1706, col. 1, lines 5-20).

Furthermore, Filion et al. (Exp. Opin. Invest. Drugs, 2001) teaches,

> "The treatment of prostate cancer has been attempted using live mycobacteria, BCG or Mycobacterium vaccae, or extracts from mycobacteria. BCG does not appear to be appropriate for the treatment of prostate cancer because of the development of the development of systemic granulomatous lesions following intraprostatic administration of the live organism or of nonviable extracts. MCC [M. phlei cell wall complex] does not appear to induce granuloma following intraprostatic administration in dogs." (See paragraph bridging pages 2160-2161.)

Indicating that not all bacterial cell wall compositions can be effective for treating all types of cancers.

Working Examples and Guidance in the Specification

The specification has working examples indicating that a composition comprising M. phlei DNA (M-DNA) which has been obtained from a disrupted mycobacterium using DNase-free reagents in order to at least partially preserve the DNA, can inhibit the growth of a human prostate tumor present in a nude mouse when the composition is directly administered to the tumor (by intratumoral injection) (see example 14, page 14).

There is no indication that a composition comprising B-DNA can effectively inhibit the growth of a prostate tumor when the composition is administered by any means other than direct delivery to the tumor (i.e., intratumoral injection of the composition).

Quantity of Experimentation

Considering the teachings in the prior art that therapeutic nucleic acid compositions are subject to immune attack by the host's immune system, and the lack of any working examples indicating that the composition can be effectively administered by any means other than intratumoral injection, additional experimentation is required. The amount of additional

experimentation required is deemed to be undue because the relevant art indicates that the problems associated with general delivery of therapeutic nucleic acids cannot be overcome by simple experimentation.

Level of the skill in the art

The level of the skill in the art is deemed to be high.

Conclusion

Considering the high degree of unpredictability related to general delivery of therapeutic nucleic acids recognized in the art, the breadth of the claims, the limited working examples and guidance in the specification; and the high degree of skill required, it is concluded that the amount of experimentation required to perform the broadly claimed invention is undue.

Response to Arguments

35 USC 102(b): Applicants argue that Morales does not teach a method of treating cancer using mycobacterial DNA (B-DNA) where the B-DNA is obtained from a disrupted mycobacterium using DNase-free reagents to at least partially preserve the DNA (see pages 8-10 of the response).

It is acknowledged that Morales does not teach that the B-DNA used in the experiments is obtained from a disrupted mycobacterium using DNase-free reagents. Considering the claims require that the B-DNA is obtained from a disrupted mycobacterium using DNase-free reagents to at least partially preserve the DNA, the rejection is withdrawn.

35 USC 103(a): Applicants argue, among other things, that neither the Morales or Filion references teach a method of treating cancer using mycobacterial DNA (B-DNA) where the B-

DNA is obtained from a disrupted mycobacterium using DNase-free reagents to at least partially preserve the DNA (see pages 10-12 of the response).

It is acknowledged that neither reference teaches a method using mycobacterial DNA (B-DNA) obtained from a disrupted mycobacterium using DNase-free reagents. Considering the claims require that the B-DNA is obtained from a disrupted mycobacterium using DNase-free reagents to at least partially preserve the DNA, the rejection is withdrawn.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Eric Angell whose telephone number is (703) 605-1165. The examiner can normally be reached on M-F (8:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

DAVE T. NGUYEN
PRIMARY EXAMINER

J. Eric Angell
May 28, 2003